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"TO STUDY LIVER FUNCTION ABNORMALITIES AND ITS PROGNOSTIC SIGNIFICANCE IN ENTERIC FEVER"

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I **Dr. Jyoti Batra** hereby declare that the present thesis **entitled "To Study Liver function abnormalities and its prognostic significance in Enteric fever" s**ubmitted by **Dr Abhishek Sharma** to Santosh university is a Bonafide/original research work. I also hereby declare that there is no plagiarism and the present research work has not been submitted for the award of any degree/diploma of the same institution where the work was carried out or to any other institution.

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LIST OF ABBREVIATIONS

S. Typhi	Serovars Typhi
S. Paratyphi	Salmonella Paratyphi
CDC	Centres For Disease Control
MIC	Minimal Inhibitory Concentration
AIDS	Acquired Immunodeficiency Syndrome
HIV	Human Immunodeficiency Virus
CBC	Complete Blood Count
SGOT	Serum Glutamic Oxaloacetic Transaminases
SGPT	Serum Glutamic Pyruvic Transaminase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
LFT	Liver Function Test
USG	Ultrasonography
MIC	Minimal Inhibitory Concentration
TMP-SMX	Trimethoprim-Sulfamethoxazole
SPI	Salmonella Pathogenicity Islands
PAI	Pathogenicity Islands
H. Pylori	Halicobacter Pylori
IgG	Immunoglobulin G
IgA	Immunoglobulin A
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
LPS	Lipopolysaccharide
MHC	Minimal Histocompatibility Complex
TNF	Tumor Necrosis Factor
TLR	Toll-Like Receptors

INTRODUCTION

Enteric fever is a major problem for people living in developing countries, including India, due to poor sanitation and faecal contamination of food and water (1). The infection is acquired through faecal-oral transmission, with the bacilli spreading from human hosts who are either suffering from enteric fever or those who are chronic carriers (2). The main etiological agent of enteric fever is Salmonella enterica subspecies enterica serotype Typhi worldwide. Other serotypes of Salmonella enterica, mainly S. Paratyphi A, B, and C, also cause enteric fever, with their incidence varying geographically (1).

In Western Countries, the disease outbreaks occur through carriers of the disease or after returning from places where the disease is endemic the so-called holiday typhoid. Such epidemics are usually rare in our country because people have developed some degree of immunity to the disease as a result of frequent subclinical/clinical infection. The regions with the maximum incidence of enteric fever (>100/100,000 cases/year) include south-central and southeast Asia, which includes India (2). Outbreaks of typhoid fever in developing countries can result in high morbidity and mortality, especially among children younger than five years of age and are caused by antimicrobial-resistant strains (2).

The typical manifestation of the disease is high fever, toxaemia, constipation during the 1st week of fever complicated by encephalopathy, and perforation during 3rd week of fever (3-5).Relative bradycardia during a high fever is an indicator of typhoid fever. Coated tongue, alteration of bowel habits varying from constipation in adults to diarrhoea in children, tender abdomen, hepatomegaly, and splenomegaly are often present (6). Agarwal et al. in their study, found clinical features of typhoid fever to confirm with earlier studies (3-5). Many reports from developing countries show that the clinical presentation of typhoid fever has significantly altered, often leading to missed diagnosis, the consequence of which is immense in terms of scarce health resources and patient suffering. Therefore its clinical spectrum requires constant reappraisal to update our physicians with current knowledge about the pattern of typhoid fever. The present study assessed the current pattern of presentation of typhoid fever and its pathological and biochemical findings (6).

Intestinal perforation and intestinal haemorrhages are typhoid fever's two most feared complications (7, 8). Neurologic complications include myelitis, cerebellitis, meningitis, and encephalitis. Typhoid fever increases the risk of abortion, especially during the first trimester (9, 10).

Typhoid hepatitis is a term coined by Osler, which was formerly known as "hepatitis typhosa," or enteric hepatitis (11). Hepatic manifestations are common in typhoid fever, in the second to fourth week of disease, enteric fever cases of hepatitis were more frequently reported (12). Symptoms of liver involvement in typhoid fever include jaundice, an increase in liver enzyme levels, hepatomegaly, and alterations in the histopathology of the liver. In addition to cases of typhoid fever, there have been reports of patients exhibiting deranged LFT suggestive of acute hepatitis, which is called as typhoid hepatitis. These symptoms include hepatomegaly, jaundice, and abnormalities in liver function tests (7). Involvement of the liver may be due to generalized toxaemia or invasion of the liver by the salmonella bacteria. Typhoid hepatitis presents a significant challenge to diagnosticians, particularly in countries where acute viral hepatitis and malaria are common (13, 14, 15). The use of proper hand washing techniques with disinfectants after defecation and prior to consuming food is an important part of the preventative measures. Through the use of these preventative measures, the risk of contracting typhoid fever will be significantly decreased. Various studies have found that an abnormal liver function test indicating hepatic involvement occurred between 23 to 60 percent of the time (16, 17, 18). As the liver has a great functional reserve, significant liver damage may have occurred without obvious clinical signs or abnormal laboratory tests. The prospective study was done to determine liver function abnormalities and to compare and evaluate them with clinical features of enteric fever.

Need for study-

Because there is a lack of access to clean water, poor sanitary conditions, and lack of adequate infrastructure for health care, enteric fever is a significant cause of mortality and morbidity in developing countries. It is an acute systemic disease with non-specific symptoms including fever, headache, malaise, abdominal pain, relative bradycardia, hepatomegaly, and splenomegaly. However, risks of complication increases without proper management. The purpose of this study is to investigate the link between duration of Enteric fever with changes in liver function.

Research hypothesis- This study will establish the order to observe the hepatic involvement during the course of enteric fever and study their clinical significance.

AIM AND OBJECTIVES

AIM - To study the liver function abnormalities and its prognostic significance in enteric fever

OBJECTIVES

- To study the liver function test abnormalities in enteric fever.
- To correlate liver function test abnormalities with clinical features of enteric fever.

REVIEW OF LITERATURE

HISTORY-

In 1880, Karl Eberth visualized Salmonella in the Peyer's patches and spleens of typhoid patients (19). Four years later, Georg Theodor Gaffky, in 1884 was able to grow the pathogen in pure culture successfully (20). A year later, a medical research expert named Theobald Smith made the discovery that would eventually become known as Salmonella enterica (var. Choleraesuis). During this period, Smith worked in the Veterinary Division of the United States Department of Agriculture as a research laboratory assistant. Daniel Elmer Salmon, a veterinarian pathologist, served as the department's administrator when he was in charge (21). At first, Salmonella Choleraesuis was believed to be the infectious agent responsible for hog cholera; hence, Salmon and Smith referred to it as the "Hog-cholera bacillus." In the year 1886, Daniel Elmer Salmon and Theobald Smith were the ones to discover S. cholera-suis, the agent that causes hog cholera (8). It was not until the year 1900 that the pathogen that had been found by Daniel Salmon's group was given the name Salmonella. Joseph Leon Lignières requested that the infection be named Salmonella in the honor of Daniel Salmon (22).

William Budd, a doctor in Bristol, while studying cholera and other intestinal fevers in 1873, demonstrated that typhoid fever can be transmitted by a specific toxin present in excrement, and its propagation was due to the contamination of drinking water by the feces of affected patients. According to Budd, every case of typhoid fever was related to another anterior case (23).

In 1880, Karl Eberth observed typhoid bacillus in mesenteric nodes and spleen of fatal cases of typhoid fever (23). The causative agent of enteric fever, termed "typhoid bacillus" was first isolated by Gaffkey in 1884, in Germany, from the spleens of infected patients (24).

In 1896, Widal and others described that the convalescent sera of infected patients caused the typhoid bacilli to lose their motility and clump together, and he termed this observation as "agglutinin." This formed the basis of the development of the Widal test (25). Pfeiffer and Kalle, in the same year (1896), developed the first typhoid vaccine using heat-killed typhoid bacilli (26). In 1900, Joseph Leon Marcel Lignieres suggested the term Salmonella for bacteria causing swine cholera in honour of Salmon**.**

In 1911, Elie Metchnikov fulfilled Koch's postulates to prove that serovar Typhi causes typhoid (23). In 1934, the first publication of the Kauffmann-White scheme was proposed based on serological analysis and listed 44 serovars (27). Antibiotics were first used to treat enteric fever by Theodore Woodward and colleagues, who described the successful treatment of this infection in Malaysian patients who were given Chloromycetin in 1948 (28). Also in 1948, K Lilleengen characterized a series of 25 clinical isolates representing different phage sensitivities, and he designated these strains as 'Lilleengen Type' using Salmonella Typhimurium, discovered genetic transduction (29). In the 1970s, epidemic typhoid fever caused by chloramphenicol-resistant strains emerged in Mexico. In 1972, Chloramphenicol resistance was reported from Calicut, India (30).

In 1973, Ames and co-workers reported Ames test that uses S. Typhimurium auxotrophic mutants to test the mutagenic activity of chemical compounds (31). No history of enteric fever is complete without the mention of "Typhoid Mary." Mary Mallon, who was born in Ireland in 1869, immigrated to the United States in 1883 or 1884 and was employed as a cook in various wealthy households in New York. During one such stint in the summer of 1906, 6 of the 11 people present in the house suffered from typhoid fever. Initially, the outbreak was attributed to the consumption of clams, but later investigations revealed Mary to be the cause. On the 15th of June 1907, George Sober, the principal investigator, published his findings in JAMA, becoming the first author to describe a "healthy carrier" of Salmonella Typhi (32). Mary Mallon was the first person to be identified as a healthy carrier in the United States. She was found to be responsible for the infection of at least 122 people, including five persons who passed away during her lifetime (33).

Etiology-

Salmonella enterica S. Typhi and Salmonella Enterica S. Paratyphi A, B, and C are the human-adapted organisms that are responsible for enteric fever (34). Salmonella Typhi is the commonest cause of enteric fever, But Salmonella Paratyphi A accounts for around 25% of cases. Salmonella subspecies are classified into >2500 serotypes (serovars) according to the somatic O antigen [lipopolysaccharide (LPS) cell-wall components], the surface Vi antigen (restricted to S. Typhi and S. paratyphi C), and the flagellar H antigen. For simplicity, most Salmonella serotypes are named for the city where they were identified, and the serotype is often used as the species designation. Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 by 0.4–0.6m. They are chemotrophs, meaning that they derive their energy from the chemical processes of oxidation and reduction of organic

compounds. In addition to this, they are known as facultative anaerobes since they are able to live both with and without oxygen (35).

Despite the fact that there is substantial geospatial heterogeneity, a number of studies have found evidence of local rises in the prevalence of S. paratyphi A in India. The incidence is also increasing in Pakistan, Nepal, and China, and some hypothesize that this may be due to higher rates of vaccination, which protects patients against S. Typhi but not S. Paratyphi A, allowing the latter to flourish. Other hypotheses suggest that the rise in incidence may be due to various factors (36). Infection with enteric fever can occur if a person consumes food or water that has been contaminated by carriers of Salmonella enterica serotype Typhi that excrete the bacteria through their feces or urine. In affluent nations, cases of this disease are rare and most often manifest in travellers who have recently returned from endemic regions. Even in industrialized nations, there is still the possibility of isolated outbreaks of an epidemic (6). In regions where enteric fever is endemic, some of the risk factors that are identified include the following: consuming food that was prepared outside the home, such as ice cream or flavoured ice drinks from street vendors; drinking contaminated water; having a close contact or relative who has recently been diagnosed with typhoid fever; living in poor housing with inadequate facilities for personal hygiene and using antimicrobial drugs in the recent past (6).

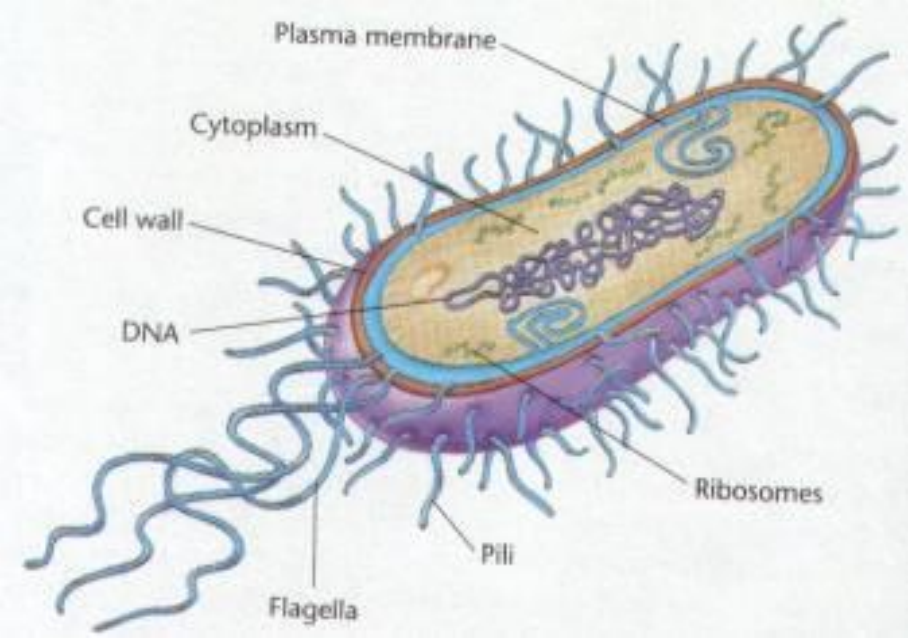

Fig 1: Salmonella Organism

TRANSMISSION-

The bacteria that causes typhoid fever can be spread by inadequate hygiene practices and circumstances of public sanitation, and in certain cases, it can also be carried by flying insects that feed on feces. One of the most critical aspects of preventing the further spread of the disease is educating the general public about the need to wash one's hands after using the restroom and before preparing or eating food. The figures provided by the Centers for Disease Control and Prevention (CDC) in the United States indicate that the chlorination of drinking water has resulted in significant reductions in the spread of typhoid fever in the country (37).

EPIDEMIOLOGY-

The etiological agent of enteric fever, Salmonella typhi and Salmonella paratyphi serotypes A, B, and C, in contrast to other Salmonella serotypes, do not have any known hosts other than humans. This is in comparison to other Salmonella serotypes. The contamination of food or water by feces from sick people or chronic carriers who are asymptomatic is the most prevalent cause of transmission through these routes. It has been documented how sexual transmission might occur between male partners. Employees in the healthcare industry may get enteric fever as a result of their contact with sick patients or their participation in the processing of clinical specimens and cultures. Enteric fever is now far less common in industrialized countries as a result of advancements in food safety practices and water and sewage treatment. On the other hand, an estimation is that there are 22 million instances of enteric fever over the world each year, resulting in 200,000 fatalities. The incidence is high in south-central and Southeast Asia (more than 100 cases per 100,000 people per year), medium in the rest of Asia, Africa, and Latin America (excluding New Zealand and Australia), and low in other regions of the world. There is a correlation between inadequate sanitation and a lack of access to clean and safe drinking water when there is a high prevalence of enteric fever. In locations where the disease is endemic, enteric fever is more prevalent in urban areas than in rural ones, as well as among young children and adolescents. the presence of risk factors like contaminated water, flooding, food and drinks from street vendors, fruits and vegetables cultivated in sewage-fertilized fields, sick household contacts, and a lack of access to clean restrooms and hand washing facilities, as well as evidence of a previous infection with Helicobacter pylori, can all increase the likelihood of contracting the disease (an association probably related to chronically reduced gastric acidity). According to estimates, there are 4 cases of typhoid fever for every 1 incidence of paratyphoid fever. Despite this, S. paratyphi A-related illnesses seem to be becoming more common, especially in India. This rise may be the effect of vaccination

for S. Typhi. S. Typhi strains that are resistant to many drugs first appeared in China and Southeast Asia in 1989. Since then, these strains have spread around the world. These strains have plasmids that code for resistance to antibiotics that have been used for a long duration of time to treat enteric fever. These drugs are chloramphenicol, ampicillin, and trimethoprim. Salmonella Typhi and S. paratyphi strains with decreased susceptibility to ciprofloxacin [MIC of 0.125-1 g/mL] have emerged in the Indian subcontinent, southern Asia, and (most recently) sub-Saharan Africa as a result of the increase in usage of fluoroquinolones in the treatment of MDR enteric fever in the 1990s. These strains have been associated with treatment failure. The majority of bacteria with reduced sensitivity to ciprofloxacin may be identified via testing of isolates for resistance to the first-generation quinolone nalidixic acid; however, this is not always the case. It is estimated that there are 3–30 cases of enteric fever for every 100,000 people who migrate from the United States.

79% of the 1902 cases of S. Typhi–associated enteric fever were reported to the Centers for Disease Control and Prevention (CDC) in 1999–2006 and were associated with recent international travel. The most common destinations for these travelers were India (47%), Bangladesh (10%), Pakistan (10%), Mexico (7%), and the Philippines (4%). Only 5% of tourists who were diagnosed with enteric fever had actually been vaccinated against S. Typhi. In the United States, the overall percent of S. Typhi isolates that were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX) was 13%. In comparison, the proportion of isolates that were resistant to nalidixic acid climbed from 19% in 1999 to 58% in 2006. Travel to the Indian subcontinent has been linked to an increased risk of infection with nalidixic acid-resistant Salmonella Typhi (NAR). The majority of the 25–30% of domestically acquired enteric fever cases that are recorded in the United States are sporadic; despite this, outbreaks linked to contaminated food products and chronic carriers that have not been previously identified continue to occur (38).

Pathogenesis-

There is a wide range of variability in the infectious dosage of S. enterica serotype Typhi in volunteers, ranging from one thousand to one million organisms. Vi-negative strains of S. enterica serotype Typhi are significantly less infectious and virulent than Vi-positive strains of the same strain. Because Salmonella enterica is acid-sensitive, it must pass through the barrier formed by gastric acid before it can infect the small intestine. A low pH in the stomach is a key defense mechanism against Salmonella (39). It has been demonstrated that during an episode

of acute enteric fever, there is a reduction in the amount of acid that is secreted by the stomach. This reduction eventually reverses itself, and the degree to which it occurs is proportional to the severity of the illness. The organism's ability to tolerate acid may be an important factor in determining whether or not it will progress to the small intestine. This ability can vary depending on the serovar that is causing the infection (40). The infective dosage of the organism is reduced when the patient has achlorhydria, which can be caused by ageing, a past gastrectomy, or therapy with histamine H2-receptor antagonists, proton pump inhibitors, or significant quantities of antacids (39). In the small intestine, the bacteria first enter the mucosa and then attach themselves to the cells of the mucosa. It is likely that S. enterica serotype Typhi is internalized and transported to the underlying lymphoid tissue in the M cells, which are specialized epithelial cells that lie over Peyer's patches. The M cells are located over the Peyer's patches (39).

After penetrating the host cell, the invading microorganisms translocate to the intestine lymphoid follicles as well as the draining mesenteric lymph nodes, and some of them go on to the reticuloendothelial cells of the liver and spleen (39).

Salmonella is able to live and reproduce inside the mononuclear phagocytic cells that are found in the lymphoid follicles, liver, and spleen. After reaching a critical threshold, which is presumably determined by the amount of bacteria, their pathogenicity, and the reaction of the host, bacteria are discharged into the circulation from their secluded intracellular home (39). In most cases, the incubation period lasts anywhere from 7 to 14 days (39).During the bacteremic phase, the bacterium has spread to a broad variety of locations. The liver, spleen, gallbladder, bone marrow, and Peyer's patches of the terminal ileum are the organs that most frequently get infected as a result of a secondary infection. Invasion of the gallbladder can occur either directly from the blood or indirectly through the bile in a retrograde fashion. The organisms that are eliminated through the bile either re-enter the body through the intestinal wall or are eliminated through the feces. The presence of 5 counts of bacteria in individuals with acute typhoid fever indicates an average concentration of 1 bacterium per milliliter of blood (approximately 66 percent of which are inside phagocytic cells) and approximately ten bacteria per milliliter of bone marrow. In spite of the fact that S. enterica serotype Typhi produces a powerful endotoxin, the death rate for patients at this stage who are treated for typhoid fever is less than one percent (39). Studies have indicated that individuals with typhoid fever have elevated amounts of both proinflammatory and anti-inflammatory cytokines circulating in their blood, as well as a decreased capacity of their entire blood to create inflammatory cytokines

when the disease has progressed to a severe stage (39). Although typhoid fever elicits humoral and cellular immune responses systemically as well as locally, these responses only provide partial protection against relapse and reinfection. In cases of severe illness, the necrosis of Peyer's patches may be caused by the interplay of immunologic mediators produced by the host with substances produced by the bacteria in the diseased tissue (39).

Salmonella pathogenicity islands, sometimes known simply as SPI, are the genetic locations on PAI that are responsible for encoding a significant number of Salmonella enterica virulence phenotypes. This comprises the virulence traits that are most noticeable, such as host cell invasion and intracellular pathogenesis. There have been a total of twelve distinct SPIs described as of right now. While some of the SPI are shared by all Salmonella strains, some are exclusive to certain serovars and cannot be found in other Salmonella strains. There are further chromosomal areas that are known as SPI. These regions have similar features of PAI, but they do not appear to have a distinct role in the pathogenesis of salmonellosis (41). Infection with typhoidal Salmonella has been linked to a wide variety of host variables, including risk factors and protective ones. It has been hypothesized that a history of infection with Helicobacter pylori is linked to typhoid fever, maybe because both disorders are linked to lower stomach acidity (40).

The existence of serum immunoglobulin G antibodies against H. Pylori were related to Enteric fever with an adjusted odds ratio (OR) of 2.03 (95% confidence interval [CI], 1.02 to 4.01) in a case-control research that was conducted in India. According to the findings of this research, being illiterate, belonging to a nuclear family, not using soap, and eating ice cream were all connected with an increased likelihood of contracting typhoid. IgG antibodies against H. pylori develop one to three months after an acute infection, and their presence can thus suggest either a current or a prior infection (42).

In a case-control research that was conducted in Jakarta, Indonesia, using an age-stratified analysis, the level of H. pylori IgG antibody was found to be greater in typhoid fever patients than in community controls. On the other hand, the level of H. pylori IgA antibody was found to be lower. In addition, the levels of plasma gastrin, which are suggestive of hypochlorhydria, were not substantially raised in typhoid fever patients in comparison to the controls (43).

There was a significant relationship between having H. pylori IgG seropositivity and having typhoid fever, with an odds ratio of 1.93 (95% confidence interval [CI], 1.10 to 3.40). This was

found by a multivariable analysis. The authors, on the other hand, noted that the linkage might be the result of common ambient exposure to poor hygiene rather than establishing a causative relationship through lower stomach acid secretion as the mechanism behind the link (40).

There have only been a few number of studies that have been able to establish host genetic variables that determine susceptibility to enteric fever. Proteins that are expressed on the mucosa of the stomach are known as CFTR, which stands for cystic fibrosis transmembrane conductance regulator. Experiments conducted in vitro have demonstrated that the wild-type protein promotes the adhesion and entrance of Salmonella serovar Typhi into intestinal epithelial cells, but Salmonella serovar Typhimurium is unable to do so. This binding and entrance are mediated by this interaction between type IVb pilus and CFTR protein residues and lipopolysaccharide (LPS) from Salmonella serovar Typhi. The cystic fibrosis transmembrane conductance regulator (CFTR) is expressed on the intestinal epithelium in response to commensal bacteria and Salmonella serovar Typhi in the colon. There is a connection between cystic fibrosis and mutations in the CFTR gene, such as F508del. When this mutation is present, Salmonella serovar Typhi does not penetrate intestinal epithelial cells, and when heterozygotes are present, Salmonella serovar Typhi uptake into intestinal epithelial cells is reduced. As a result, the F508del mutant has the potential to offer protection against infection after being exposed to the Salmonella strain Typhi (40).

It's likely that cellular immunity plays at least some role in the immune response to enteric fever. There are associations between enteric fever and the MHC class II and class III genes, according to a research commissioned in Vietnam. Among hospitalized patients, the alleles of HLA-DR, HLA-DQ, and the proinflammatory gene TNFA were related to either resistance or susceptibility to enteric fever. In patients with enteric fever, circulating levels of tumor necrosis factor-alpha (TNF-a) and soluble TNF receptor were found to be raised, with the elevation being greater in patients with more severe illness (40). The reactions of the innate immune system to bacterial infections are mediated by proteins called toll-like receptors (TLRs). TLR5 is able to bind to bacterial flagellin, while TLR4 is able to attach to LPS (40).

Liver Involvement in Enteric Fever-

A relatively new term, salmonella hepatitis, was established to describe the hepatic complications of Enteric fever. It is a distinct entity that presents clinically and diagnostic tools. Salmonella hepatitis is a condition that can mimic acute viral hepatitis, making its diagnosis extremely important in the clinical setting (44,45). The prognosis for these

individuals can be improved by beginning targeted therapy as soon as possible after an early diagnosis.

In accordance with the recommendations made by the Pakistan Society of Hepatology in 2017, a patient is considered to be suffering from Salmonella hepatitis (also known as typhoid hepatitis) if he or she meets three or four of the following criteria (46, 47, 48). (a) Hepatomegaly, (b) Jaundice, (c) Biochemical abnormalities - serum bilirubin > 30.6 umol /l, SGOT/SGPT should be increased with or without 5'adenosine nucleotides and/or prothrombin time prolongation, and/or (d) Abnormal liver histopathology. In endemic regions, involvement of the liver in typhoid is more prevalent, but it has been documented in non-endemic regions as well. The incidence of acute hepatitis in patients caused by Salmonella ranges from 1% to 26% (47). There is no age group that is immune to typhoid hepatitis; nevertheless, individuals who come from lower socioeconomic classes and those in their second to fourth decade are more likely to have the condition (48). Complications such as hepatitis are more common in people who have a weak cellular immune system and in those who have experienced recurrent episodes of typhoid fever.

Although the incidence of salmonella hepatitis seems to be more common in adult male patients, it can also occur in elderly people. There are no definitive predisposing factors that can put someone at risk for salmonella hepatitis. There is a lack of understanding regarding the pathogenesis of salmonella hepatitis. Malnourished individuals who are members of lower socioeconomic groups are more likely to exhibit this condition (49). Because bacteremia is present in the majority of individuals with typhoid fever, liver damage may be attributable to this condition. Salmonella endotoxin, along with other aspects of typhoid fever, has been suspected of playing a role in the development of salmonella hepatitis. When these bacilli reach the blood, which happens after significant proliferation in the lymphoid tissue of the colon, they are destroyed, which results in the release of endotoxin, which is what causes the symptoms of typhoid fever. The potential role that arteritis and localized intravascular coagulation play in the aetiology of clinical characteristics associated with typhoid fever. Hepatic harm might be caused by vascular hyperactivity because of catecholamines. Typhoid fever has been associated with immune complexes and a high antitrypsin-to-C3 ratio; these manifestations are more frequent in people who also have complications such as hepatitis (50). Histopathologically, Salmonella hepatitis is characterized by cloudy swelling, ballooning, degeneration with vacuolation, moderate fatty change, and mononuclear cell infiltration in a few focal areas, but there is no focal necrosis. On the other hand, viral hepatitis is characterized

by acute diffuse inflammation with necrosis of the liver cells but without any fatty change. Both the symptoms of typhoid fever and those of hepatic involvement would be present in the clinical picture. In the majority of instances, the start of fever associated with typhoid is delayed and subtle; nevertheless, fast onset of fever, with or without chills, has sometimes been recorded (51). Headaches, a general feeling of malaise, and loss of appetite are the prodromal symptoms that occur most frequently before to the actual beginning of fever (52,53). It is possible to have chest symptoms such as a cough and sore throat, as well as stomach discomfort, constipation, diarrhea, abdominal distension, body aches and pains, and abdominal distension. Some of the typical visible symptoms of typhoid include fever, relative bradycardia, toxaemia, typhoid tongue, splenomegaly, hepatomegaly, rose spots, and abdominal discomfort (54). Hepatomegaly, jaundice, abnormal liver function tests, and abnormal histology are all signs that indicate hepatic involvement, and any one of these symptoms might be present on its own or in conjunction with the others (55). Salmonella hepatitis is typically moderate and has a benign course, and it may even be missed by the physician. On the other hand, it can be severe and present with symptoms such as severe bleeding syndrome, hematemesis, or hepatic encephalopathy. Individuals who have hepatic encephalopathy due to Salmonella typically do not exhibit symptoms such as asterixis or hepatic flap, in contrast to patients who have hepatic encephalopathy due to other causes (56).

CLINICAL FEATURES-

The symptoms of enteric fever, which include fever and gastrointestinal discomfort, are characteristic of this condition. The incubation period for S. Typhi typically lasts between 10 and 14 days, although it can last anywhere from 3 to 21 days depending on the quantity of the inoculum, as well as the health and immunological condition of the host. The most noticeable symptom is a high temperature that lasts for a long time (38.8–40.5°C; 101.8–104.9°F), which can last for as long as four weeks if it is not treated. It is believed that S. paratyphi A causes an illness that is less severe than S. typhi, with symptoms that focus mostly on the digestive tract. On the other hand, a prospective research conducted in Kathmandu, Nepal, involving 669 consecutive instances of enteric fever, indicated that the infections were clinically indistinguishable from one another. Myalgia (20%), malaise (10%), arthralgia (2–4%), and headaches (80%) were reported as symptoms at the initial medical assessment for this series. Other symptoms were chills (35–45%), cough (30%), sweating (20–25%), and myalgia (20%). Anorexia (55%), stomach discomfort (30–40%), nausea (18–24%), diarrhea (22–28%) and vomiting (18%) occurred more frequently than constipation (13%–16%) among those who

experienced gastrointestinal symptoms. Coated tongue was one of the physical signs in 51–56% of patients, along with splenomegaly in 5–6% and stomach pain in 4–5%. Early signs of enteric fever include a rash (also known as "rose spots" and occurring in thirty percent of cases), Hepatosplenomegaly (occurring in three to six percent of cases), epistaxis, and relative bradycardia during the peak of high fever in fifty percent of cases. Rose spots are characterized by a scaly rash that is pale, salmon-colored, maculopapular, and blanching. They are most commonly found on chest and trunk. The rash becomes visible in thirty percent of patients by the end of the first week and disappears completely between two and five days later. Patients may experience two or three separate crops of lesions, and Salmonella can be cultivated from punch biopsies taken from any of these lesions. Because the rash is so subtle, it might be difficult to identify in people with a high level of pigmentation. The host factors (immunosuppression, antacid treatment, previous exposure and vaccination), virulence of strain and inoculum, and choice of antibiotic therapy all have a role in the development of severe illness, which happens in 10–15% of patients. This development can be prevented by immunisation. Gastrointestinal bleeding in 10–20% and intestinal perforation in 1–3% cases most commonly occur in the 3rd and 4th weeks of illness and at the initial site of Salmonella infiltration, the ileocecal Peyer's patches exhibited hyperplasia, ulceration, and necrosis. This happens when the ileocecal Peyer's patches become infected with Salmonella. Both complications pose a significant risk to a patient's life and require immediate treatment with fluid resuscitation and surgical intervention. In the case of polymicrobial peritonitis and treatment of gastrointestinal hemorrhages, which may include bowel resection, antibiotic coverage should be expanded. Meningitis, neuritis, Guillain-Barré syndrome, and neuropsychiatric symptoms, such as picking at phantom objects or bedclothes and termed as "muttering delirium" or "coma vigil," are a few examples of the neurologic manifestations that can happen in 2-40% of patients. Neurologic manifestations include the following (57).

COMPLICATIONS-

The two most worrisome typhoid fever complications are intestinal perforations and haemorrhages (58). Overall, each affects 5% or fewer of adult typhoid fever cases and somewhat less of children (59). Intestinal perforation and intestinal bleeding were reported to occur in 13.1% and 4.7% of typhoid patients, respectively, in a prior report from Durban, South Africa (60). In general, 2-3% of typhoid patients experiences a recurrence days or weeks after their illnesses appear to be cured (61, 62). About 2-3% of people who have typhoid fever develop chronic carriers (63) these people will excrete S. Typhi over a period of several years

mainly in the feces, occasionally in the urine, without displaying systemic symptoms of typhoid fever (64). In typhoid-endemic locations where urinary schistosomiasis and gallbladder disease are also prevalent, chronic typhoid carriers are frequently observed (65). Relapse and chronic carrier status for S.typhi are anticipated to be more common in AIDS patients with typhoid fever, as has been seen with non-typhoidal Salmonella (66). The scientific validity of such a claim is plausible given that the hepatic Kupffer cells play a vital role in clearing circulating microorganisms (67) and that this clearing function is impaired even during the asymptomatic stage of HIV infection. There doesn't appear to be any published data in the English language literature, other than from a research from Peru (68), that indicates a higher prevalence of either typhoid fever relapses or chronic S. Typhi carrier ship in AIDS patients with typhoid fever. It is obvious that chronic carriers provide a risk to the population (69, 70). In 1% of typhoid patients, radiologically confirmed pneumonia, mostly bronchopneumonia develops (71). In 12% of typhoid fever patients, electrocardiographic signs of myocarditis with longer P-R and Q-Tc intervals and T-wave alterations may be seen (72). A palpable liver and clinical jaundice associated with typhoid hepatitis have been seen in 0.4% to 8.3% of individuals (73-77).Glomerulonephritis can sometimes worsen the clinical course of typhoid fever (77, 78). (Associated with or without acute renal failure or acute tubular necrosis). Although renal biopsy is seldom conducted in this patient population, the real prevalence of these in typhoid patients is unclear (79). Myelitis (6%), cerebellitis (1.1%), meningitis (0.5%), and encephalitis (0.3%) are among the neurologic consequences (80,81). Abortion risk is increased by typhoid fever, especially in the first trimester (82,83). Numerous investigators have expressed their suspicions regarding S.typhi intrauterine transmission (84). Haemolytic anaemia is usually a complication of typhoid fever among ethnic African populations (85). Typhoid fever cases in whose clinical courses have been worsened by circulatory failure are described in certain publications (86) from Asia. Typhoid fever clinical courses might infrequently become complicated in the pre-chloramphenicol period by cholecystitis, arthritis, osteitis, and myositis. These problems are observed quite seldom these days (87).

Treatment-

For a while, ciprofloxacin and ofloxacin, two fluoroquinolones, were the go-to medications for enteric fever. However, resistance to these medications has increased significantly in South Asia, with isolated reports of the same in sub-Saharan Africa. Current disc susceptibility breakpoints cannot identify ciprofloxacin-resistant strains, although they are typically nalidixic acid-resistant. All enteric fever pathogens isolated from South Asia must be tested for nalidixic

acid sensitivity, and ciprofloxacin should not be administered if resistance is found. Enteric fever should be treated with gatifloxacin (10 mg/kg), azithromycin (10 mg/kg), or ceftriaxone (1-2 g/day). Recent unpublished studies have demonstrated the relative inefficacy of cefixime, an oral third-generation cephalosporin that the WHO recommends for the treatment of enteric fever, in compared to gatifloxacin, a new generation fluoroquinolones (88).

Gatifloxacin is a new relatively cheaper broad-spectrum synthetic 8-methoxyfluoroquinolone antibiotic with once-daily oral administration. It has the lowest minimum inhibitory concentration (MIC) of any antibiotic against S. Typhi from Nepal and Vietnam (88). For the treatment of enteric fever in the underdeveloped world, it seems to be successful. Even with a significantly reduced sensitivity to the earlier fluoroquinolones, gatifloxacin's unique binding motif definitely permits it to retain effectiveness against S. enterica serovar S Typhi and Paratyphi A (88).

Olfloxacin, even at greater dosages (20 mg/kg), is no longer efficacious, but azithromycin and gatifloxacin seem to be similarly effective as oral medicines. Despite in vitro resistance to S. enterica serovar Paratyphi A being demonstrated, ceftriaxone is beneficial as a parenteral drug. It has been challenging to identify azithromycin resistance, in part because of its high intracellular concentration (88).

Despite S. enterica appearing to be responsive in vitro, gentamycin has little impact on enteric fever. According to anecdotal evidence, isolates are once again becoming susceptible to older medications like chloramphenicol, which is highly encouraging news in regions of South Asia where chloramphenicol is very affordable. In areas of endemicity without blood cultures, antibiotic therapy for typhoid fever is frequently begun empirically on the basis of the syndrome of fever for three or four days with constitutional symptoms and no known source of infection. In such a situation, concurrent doxycycline treatment to treat typhus and leptospirosis may also be required. Malaria may also need to be checked out. We need to utilize what we now have as efficiently as possible since the prospect of new enteric fever medications is not encouraging due to the small number of potential targets in Salmonella that new medications may be developed against (88).

Less than 5% of typhoid patients have perforation of ileal ulcers, which is characterised by agitation, hypotension, and tachycardia. Treatment consists of fluid correction and quick surgery, which, in some series, results in a survival rate of over 97%, as opposed to approximately 30% in patients who get conservative management (88).

Contrary to the notion that Paratyphi A was a milder illness, recent findings indicate that the clinical symptoms and complication rates in Typhi and Paratyphi A infections are comparable. Therefore, paratyphoid fever treatment must be administered with the same vigour as a typhoid fever treatment (88).

PREVENTION AND CONTROL -

Salmonellae that cause enteric fever may theoretically be eradicated since they can only survive in human hosts and are dispersed through tainted food and water. This objective is now unattainable because of the high incidence of the disease in underdeveloped nations with inadequate sewage disposal and water treatment. Therefore, visitors visiting underdeveloped nations should be urged to carefully watch their food and water intake and to think about immunization. There are two commercially available typhoid vaccines: Vi CPS, a parenteral vaccine made of pure Vi polysaccharide from the bacterial capsule, and Ty21a, which is an oral live attenuated S. Typhi vaccine given on 1, 3, 5, and 7 days and a booster every five years, whereas Vi CPS given in 1 dose, with a booster every two years. Due to serious adverse effects, the outdated parenteral whole-cell typhoid/paratyphoid A and B vaccination are no longer approved (see below). Only the U.S. military may utilize a whole-cell vaccination that has been destroyed by acetone. For Ty21a and Vi CPS vaccine eligibility requirements are six years old and two years old, respectively. There isn't an approved vaccination available for paratyphoid fever right now. According to a large-scale meta-analysis of vaccine trials comparing whole-cell vaccine, Ty21a, and Vi CPS in populations in endemic areas, all three vaccines are equally effective for the first year, but the whole-cell vaccine has a higher 3-year cumulative efficacy (73%) than Ty21a (51%) and Vi CPS (55%), despite being less effective overall. Additionally, compared to Ty21a and Vi CPS, which keep their efficacy for 4 and 2 years, respectively, and the heat-killed whole-cell vaccine, which maintains its efficacy for five years. However, compared to the other two vaccinations, the whole-cell vaccine has a substantially greater rate of adverse effects, particularly fever (16% vs. 1-2%). Due to its T cell-independent characteristics, the Vi CPS typhoid vaccine has a weak immunogenicity in children under the age of 5.Vi is coupled to a harmless recombinant protein that is equivalent to Pseudomonas aeruginosa exotoxin A in the recently created Vi-rEPA vaccine.

Two Vi-rEPA injections in 2- to 4-year-olds resulted in greater T cell responses and serum IgG antibody levels to Vi than Vi CPS did in 5- to 14-year-olds. Vi-rEPA demonstrated 91% effectiveness at 27 months and 88% efficacy at 43 months in a two-dose experiment in Vietnamese children aged 2 to 5 years. It was also highly well tolerated. The United States

does not now have access to this vaccination commercially. At least three novel live vaccinations are now undergoing clinical testing and might be more effective and durable than earlier live vaccines. Despite the fact that getting the typhoid vaccine is not required for international travel, those who are going to areas with a moderate to high risk of exposure to S. Typhi, such as southern Asia and other developing regions of Asia, Africa, Central and South America, the Caribbean and who will be exposed to potentially contaminated food and drink, should get the vaccine. Even those travelling for less than two weeks to high-risk regions should think about getting the typhoid vaccination. Additionally, those who work in laboratories where S. Typhi is present, as well as household members of known S. Typhi carriers should receive vaccinations. Because the protective benefits of vaccinations can be negated by the high inoculate that are typically seen in food-borne exposures, vaccination is an adjuvant and not a substitute for avoiding high-risk meals and beverages. Adults living in typhoid-endemic regions and anyone who may have been exposed during a common source epidemic are not advised to get immunized. In the US, enteric fever is a prevalent illness. Each health department has its own policies on the return to work of sick or colonized food handlers or healthcare professionals. In order to treat chronic carriers and identify probable source patients, public health agencies can use the reporting system to stop new outbreaks. Additionally, it is crucial to monitor patients for chronic carriage of S. Typhi infection and to treat this disease if necessary. This is especially critical for those who work with children or who handle food (89).

SRIKANTH N. MD et al. Out of 50 instances of enteric fever, 2 cases in the first week, 13 cases in the second week, and 7 cases in the third week had raised AST levels by more than two folds. A statistically significant correlation exists between AST levels and fever duration (x2 7.2219; df = 2; P 0.05). Serum ALT was normal in 29 patients, high (more than 2 fold) in 21 out of 50 patients (42%), and normal in 29 patients. In 2 instances in the first week, 12 cases in the second week, and 7 cases in the third week, an ALT range of 3 U/L to 368 U/L was recorded. The association between the duration of the fever and the ALT levels is statistically significant (x2 = 6.3557; df -2; P 0.05). Serum alkaline phosphatase (ALP) levels ranged from 13 U/L to 628 U/L, were normal in 31 individuals, and were raised by more than 2 times in 19/50 (38%) patients. ALP levels were found to be increased in 2 instances in the first week, 11 cases in the second week, and 6 cases in the third week, out of 50 cases of enteric fever. Serum alkaline phosphatase and fever duration are statistically significantly correlated.

In a research from Al-Sader Teaching Medical City in Najaf, Iraq, the liver function and blood levels of pro-inflammatory cytokines (IL-6 and IL-8) were assessed in 120 typhoid fever patients (males and females) aged 20 to 50 and 60 healthy persons in the same age range as a control group. Alkaline phosphatase (ALP), alanine transaminases (ALT), and aspartate transaminases (ALT) mean serum levels were, respectively, 130±9.8IU/l, 31.4±5.9IU/l, and 26.8±4.2IU/l in Typhoid fever patients ($P<0.05$ for each). Additionally, the patient's levels of IL-6 (157±5.2 pg/ml), IL-8 (136±7.1 pg/ml), and C-reactive protein (CRP) (41±3.4 mg/l) were significantly higher than those of healthy individuals (40±6.3 pg/ml, 37 ±5.9 pg/ml, and 9 ±2.2 mg/l, respectively) ($P<0.001$). Salmonella Typhi has been reported to cause hepatic involvement. In a study on hepatic involvement with typhoid fever, nine patients were studied with positive blood cultures in order to identify characteristic features of typhoid hepatitis which may help in early diagnosis. Patients who had an illness resembling enteric fever but negative cultures for Salmonella Typhi were excluded. Liver function tests showed a wide range of variability, and no specific clinical features were consistently detected. Due to vomiting and renal involvement, further biochemical abnormalities developed. A liver biopsy revealed non-specific inflammation and focal hepatocellular necrosis. Although most responded to conventional antibiotics, it was generally a delayed response. It is recommended that patients with fever greater than 38.5°C and liver abnormalities should undergo blood, urine, stool and/or bone marrow cultures.

Jain H. Et al has done a study in the paediatric age group, diagnosing enteric fever on the basis of clinical features, confirmed by Widal test and LFT was performed to assess liver involvement. Where hepatomegaly was seen in 35% cases and tender hepatomegaly was seen in 2 cases of the study group. S.G.O.T was raised in 50% cases and S.G.P.T was raised in 46% cases. Most of the cases with raised S.G.O.T and S.G.P.T presented in the 2nd week of fever.

S. Bhatia et al conducted a study in 111 patients with enteric fever, of which 56 patients (50%) were diagnosed with typhoid fever and 55 patients (50%) were found to have paratyphoid fever. The most common abnormality observed was deranged liver enzymes more notably in patients presenting beyond the second week of illness; AST levels were abnormal in 93 patients (82%).

Ashish Kakarial et al had studies clinical profile of enteric fever patients in western India74. In the study incidence of fever 100%, chills 26%, vomiting 44%, diarrhoea 28%, abdominal pain 64%, headache 26%, and signs as splenomegaly 36%, hepatomegaly 42%, rose spots 6%,

relative bradycardia 34% were reported. Anaemia, leukocytosis and leukopenia and elevated liver enzymes were found in 42.9%, 10%, 21% and 45% respectively.

Najla abdulameer ali Al dahaan et al. did a research in Iraq where they looked at the relationship between liver function and patients with typhoid fever. The results showed that there was a significant rise ($P < 0.05$) in the blood levels of the liver enzymes ALP, ALT, and AST. 120 patients with clinical signs of typhoid fever and positive results from both the Widal test with increasing titer and the typhoid IgG/IgM rapid test device, an in vitro-based immunological method for the identification of IgG and IgM in human blood, serum, or plasma, were included in the study by **Hulal Saleh Sahib et al.** There were 54% men and 46% women. Every patient had a fever, headache, and Vomiting, 40% anorexia, and 27% jaundice. On clinical inspection, there were 26% jaundice, 18% hepatomegaly, and 4% hepatosplenomegaly. Most typhoid patients have abnormal biochemical testing, including high ALT levels of 25%, AST levels of 18%, and ALP levels of 16%.

MATERIAL AND METHODS

Study Place: The study was conducted in Department of Medicine, Santosh Medical College and hospital, Ghaziabad

Study Design: Cross-sectional Observational Study

Study frame: Study was done in patient presented with fever, chills, pain abdomen, nausea, vomiting, diarrhea who attended Medicine OPD and IPD of Santosh Hospital.

Inclusion criteria:

- Study population attended medicine OPD and IPD.
- Age $\geq$ 18 years
- Both genders were included
- Patients of enteric fever diagnosed on the basis of clinical history, physical examination, blood culture, Typhi dot IgM and Widal test.

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Exclusion criteria:

- Pediatric patients with enteric fever.
- History of alcohol consumption.
- History of hepatotoxic drug abuse.
- Positivity for markers of hepatitis viruses.
- History or clinical evidence of chronic liver disease, gallstones and coexistent disease.
- Hepatitis B antigen positive.

Diagnostic criteria:

The diagnosis was confirmed by the following investigation:

- **Serum widal reaction –** the widal reaction will be considered as positive when -
    - i. Titre with O antigen of more than 1/80 dilution.

- ii. A titre of 1/120 or more with B.typhosum H antigen and no agglutination with other antigens.

- **<u>Liver function tests</u>:**

  i. Serum bilirubin – total, direct and indirect.
  ii. Serum proteins – total, albumin and globulin.
  iii. Serum glutamic oxaloacetic transaminase [SGOT] and serum glutamic pyruvic transaminase [SGPT] estimation .

Sample size-

In this study, as we want to study LFT abnormalities in cases of Enteric fever. Therefore, in order to calculate the sample size, we need to have the estimated prevalence of Enteric fever.

To this reference, we have found that past researches have reported the prevalence of Enteric fever in India ranging from 27.8% to 44%. Taking the higher limit of 44%. On calculating the sample size, using these values and the sample size formula with the correction factor by Fleiss given below:

- Sample size: $\mathbf{n = Z\ alpha^2 P(1\text{-}P)/d^2}$
- $Z\alpha = 1.96$ at 5% level of significance
- P= prevalence of Enteric fever (i.e.44%)
- d= relative error (i.e.10% of P)
- Our sample size based on above calculation (cases-94)
- **Cases:** Minimum 94 cases were required for this study as per the Statistical analysis of the data, a total of 100 patients were took for this study attending Medicine OPD and IPD in the age group of 18 year above will be subjected to History, Physical examination, Routine investigations, Special investigations.

Subject Confidentiality:

Data collection was on paper. The patients participating in the study was contacted only by the persons involved in the study. All the patient specific data was kept in strict confidence. Patient identifiable data (name, contact, address, etc.) will not be presented in journal or any public forum.

Informed Consent:

Informed consent process was initiated prior to the individual agreeing to participate in the study and continuing through out the individual's study participation. The form provided had all the information required for the patient to understand their role in the study. It was in a language understandable by each member of the study population. It was submitted for the ethical committee clearance.

Financial Inputs and Funding:

All the study related procedures and investigations were done according to the institutional protocol. All these expenses were borne by the patient. Also, this study was not being sponsored by any pharmaceutical company.

Ethical Considerations:

The protocol of the present study was submitted to the Ethics Committee of Santosh Medical College & Hospital for review. After getting their approval the study was initiated in the institution. Also prior to enrolling any patient in the study, a voluntary written informed consent was obtained for participation.

METHODOLOGY

The data collection was included in a detailed clinical history, examination, investigations, follow up, the treatment given and complications observed. A past history of fever was looked. A detailed clinical examination was carried out particularly for the presence of jaundice, pallor, hepatosplenomegaly, altered sensorium, perforation and bleeding tendencies.

The Investigations done included:

1) **Liver function test (**using IFCC and PNPP method) was done which included total proteins, albumin, total and direct bilirubin, aspartate amino transferase, alanine amino transferase, alkaline phosphatase.

2) Blood Culture (using BACTEC-FX method).

3) **Widal test** (using slide agglutination method), Chest X-ray, Peripheral smear for malaria parasite, and Hepatitis B surface antigen.

4) Complete haemogram (by Cell counter method).

5) Urine for routine examination.

6) Routine blood tests for sugar, urea and creatinine (by Urease and JAFFE method), Ultrasonography of abdomen was done in clinically indicated cases.

7) **Criteria for Salmonella hepatitis**

- Jaundice present either clinically or total bilirubin more than 1.8 mg/dl.
- Hepatomegaly (Liver span > 14 cm) either clinically or by ultrasound examination.
- Elevated liver transaminases more than two times or prolonged prothrombin time.
- Abnormal liver pathology.

Any 3 of the 4 criteria should be fulfilled for making the diagnosis of salmonella hepatitis.

Data management and Statistical Analysis:

The data will be collected and entered in MS excel 2010. Different statistical analysis will be performed using R software version 4.0.2. The one-sample Kolmogorov – Smirnov test will be employed to determine whether the data sets differed from a normal distribution or not. Normally distributed data will be analyzed using parametric tests and non - normally distributed data will be

analyzed using non parametric tests. Descriptive statistics will be calculated for qualitative and categorical variables. Graphical representation of the variable will be shown to understand the results clearly and to measure the association for categorical dataset will be analyzed using Chi-Square test. Independent T-test or student t-test will be applied to measure the mean difference between two groups. Correlation will be estimated to measure the strength of relationship between two or more quantitative variables. If p value <0.05, considered as statistically significant. If p value >0.05, then it is statistically insignificant.

RESULTS AND OBSERVATIONS

The present study was conducted in Department of Medicine, Santosh Medical College and hospital, Ghaziabad with the objective to study the liver function test abnormalities in Enteric fever patients. 100 adult patients diagnosed as having enteric fever were enrolled in the study.

Table 1: Distribution of patients according to gender

Sex	Frequency	Percent
Male	56	56.0%
Female	44	44.0%

This table shows Out of 100 patients 56 were male and 44 were female

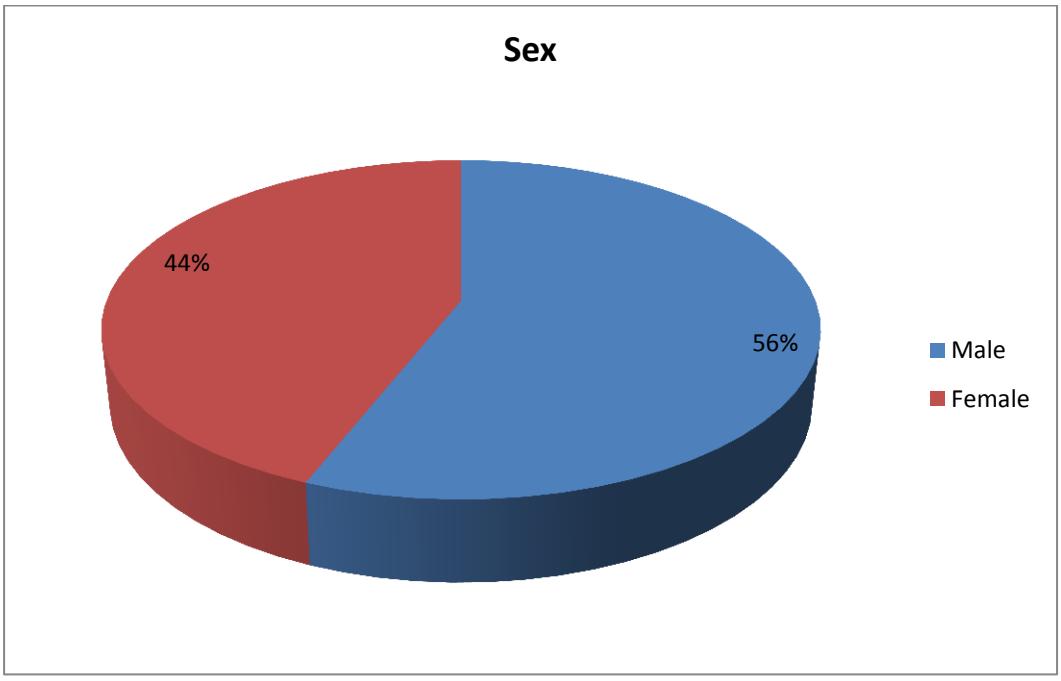

Figure 1: Distribution of patients according to gender

Table 2: Distribution of patients according to Typhoid/Paratyphoid

Widal test	Frequency	Percent
Typhi	96	96.0%
Paratyphi	4	4.0%

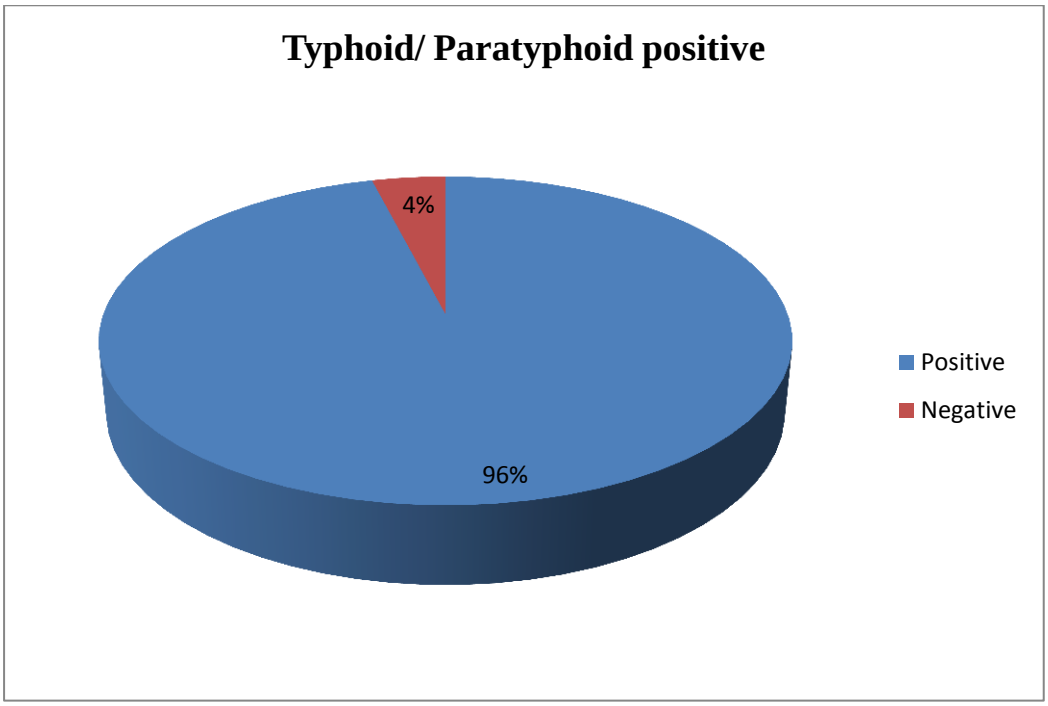

Figure 2: Distribution of patients according to Typhoid/Paratyphoid

Table 2- Here 94 cases were Typhoid positive and only 4 cases were paratyphi positive

Table 3: Distribution of patients according to symptoms

Symptoms		Frequency	Percent
Fever	Positive	100	100.0%
Pain abdomen	Positive	42	42.0%
Vomiting	Positive	40	40.0%
Loose stools	Positive	35	35.0%

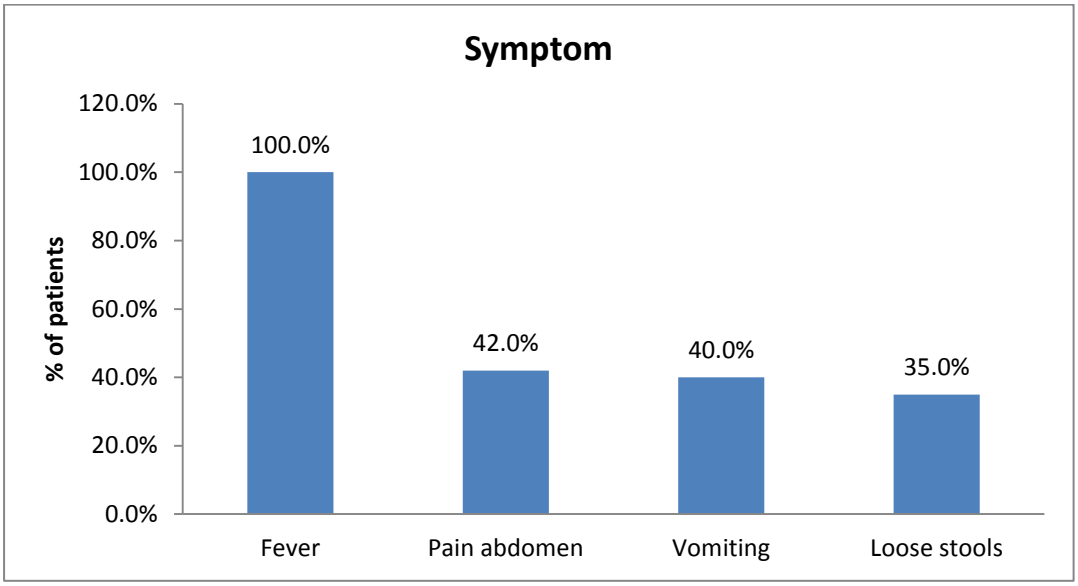

Figure 3: Distribution of patients according to symptoms

Table 3- Being classical symptom of enteric fever, Fever is the presenting symptom in all patients. High grade fever is present in considerable number of patients (70%), while only 30% patients had low grade fever. 70% patients had chills and only 30% had rigors with fever. Classical pattern of enteric fever is stepladder type which was seen in 64% of study population. Other patterns observed are intermittent and continuous type. G.I. Tract is the most common involved system with symptoms like vomiting, abdominal pain, diarrhoea, and constipation where almost half of patients had abdominal pain.

Table 4: Distribution of patients according to signs

Signs	Frequency	Percent
Relative Bradycardia	12	12.0%
Toxic Look	100	100.0%
Icterus	1	1.0%
Hepatomegaly	39	39.0%
Splenomegaly	6	6.0%
Altered sensorium	1	1.0%

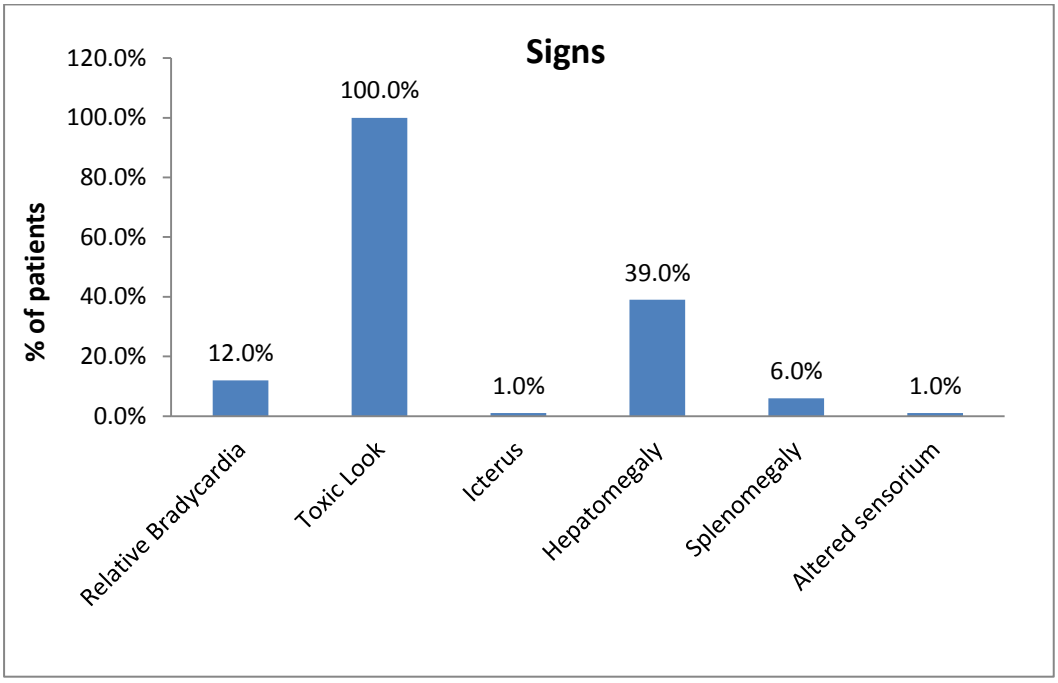

Figure 4: Distribution of patients according to signs

Table 4 - On examination, all the patients had toxic look, 39 patients had hepatomegaly, 12 patients had relative bradycardia, 6 patients had splenomegaly and 1 patient had altered sensorium.

Table 5: Distribution of patient on the basis of Liver function

Liver Function Test	Frequency	Percent
ALT	41	41.0%
AST	46	46.0%
ALP	38	38.0%
Sr. Bilirubin	7	7.0%

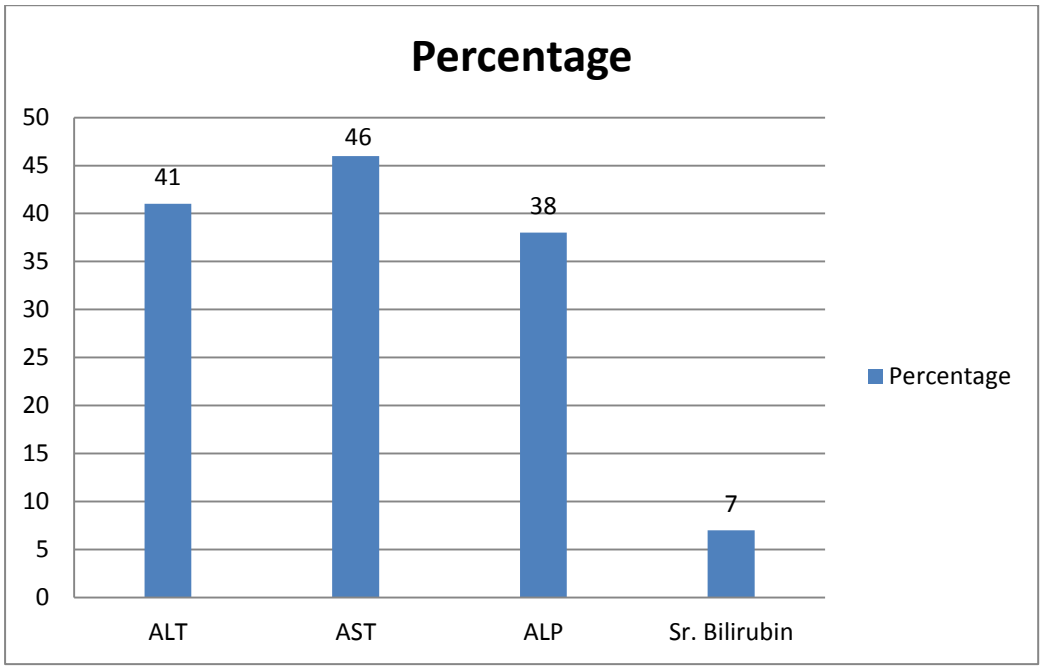

Figure 5: Distribution of patient on the basis of Liver function

Table 5 - shows the distribution of LFT abnormality in various parameters, showing deranged AST in 46% patients, deranged ALT in 41% patients, deranged ALP in 38% patients and deranged S. Bilirubin in 7% patients.

Table 6: Shows distribution of complications in Enteric fever patients

Complications	Frequency	Percent
No complications	91	91.0%
Hepatitis	5	5.0%
Encephalopathy	1	1.0%
Pneumonia	3	3.0%

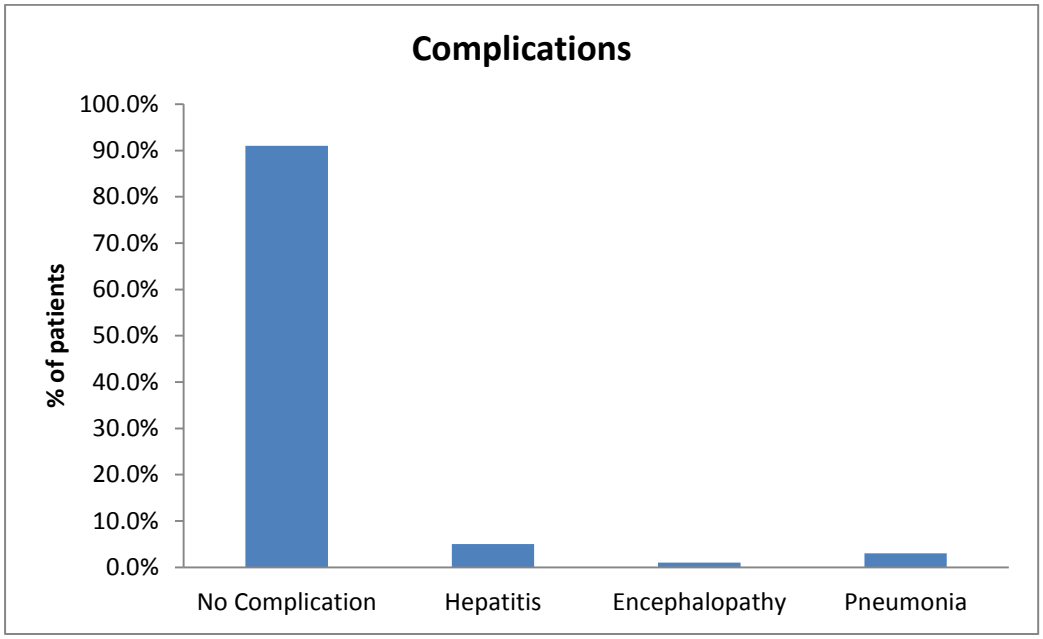

Figure 6: Shows distribution of complications in Enteric fever patients

Table 6 - shows there is no complications in 91 patients, 5 patients had hepatitis, 3 patients had pneumonia and 1 patient had encephalopathy

Table 7: LFT abnormalities with symptoms of the patients

Symptoms	No. of patients	Deranged LFT	Percentage	p-value
Fever	100	46	46.0%	0.256
Pain abdomen	42	16	38.1%	.025*
Vomiting	40	18	45.0%	0.369
Stool	35	15	42.9%	0.227

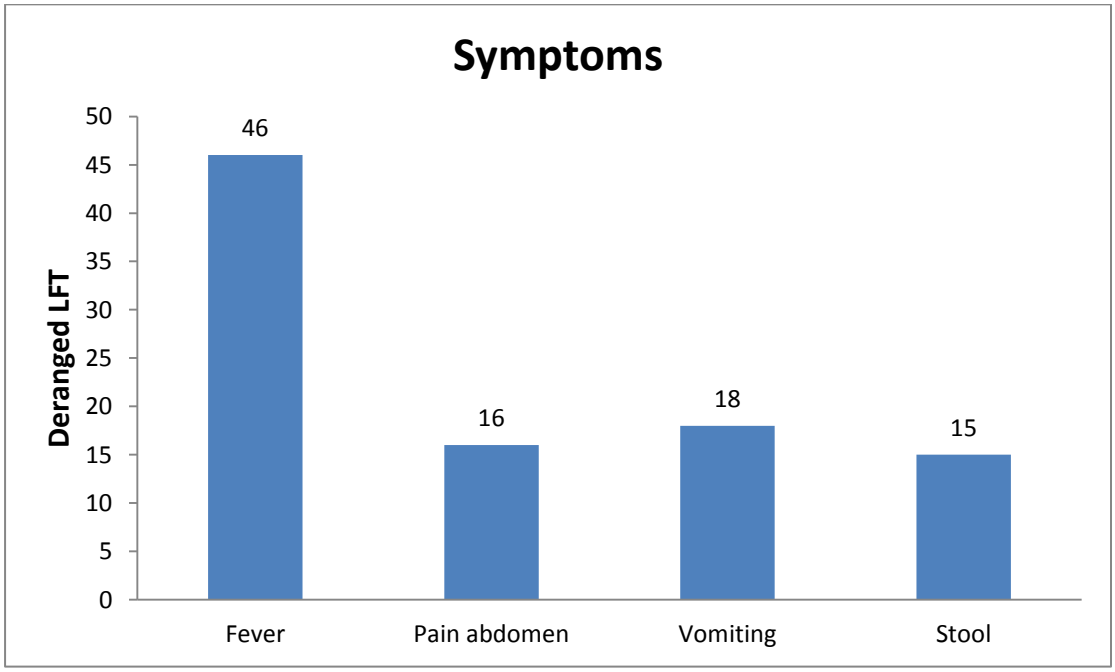

Figure 7: LFT abnormalities with symptoms of the patients

Table 7 - shows deranged LFT was found in 46 patients of fever, 16 patients of pain abdomen, and 18 patients of vomiting and 15 patients of loose stool.

Table 8: Shows patients with deranged LFT according to signs

Signs	No. of patients	Deranged LFT	Percentage	p-value
Bradycardia	12	6	50.0%	1
toxic look	100	46	46.0%	0.256
hepatomegaly	39	32	82.1%	.0001**
Splenomegaly	6	5	83.3%	.002**
Icterus	1	1	100.0%	1
altered sensorium	1	1	100.0%	1

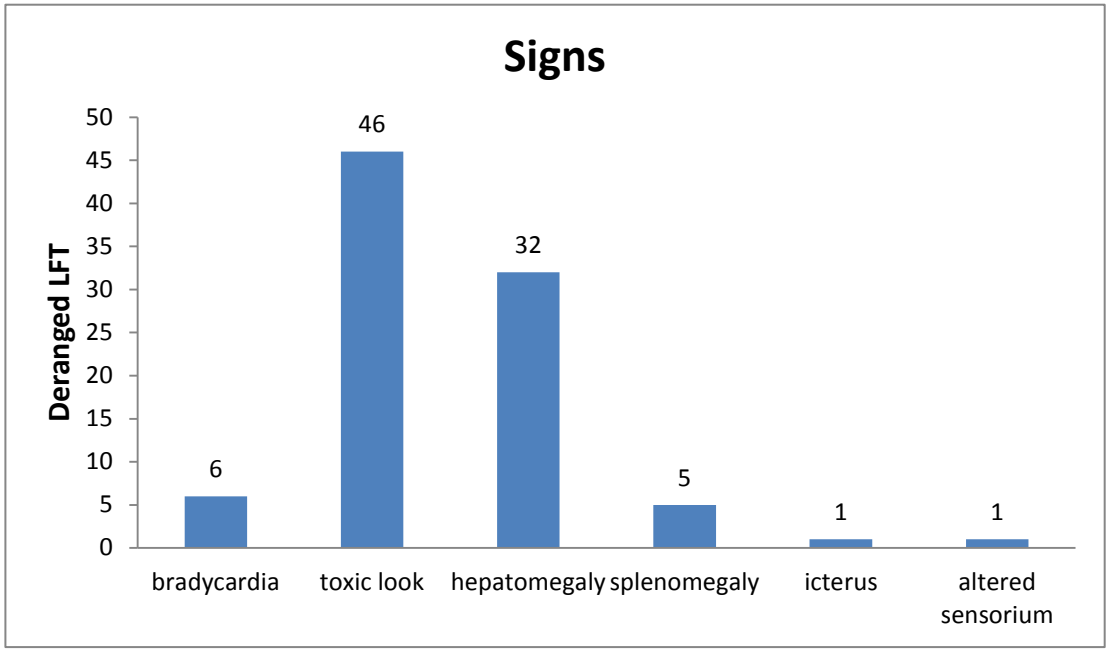

Figure 8: Shows patients with deranged LFT according to signs

Table 8- shows in patients with deranged LFT 6 patients had Bradycardia, 46 had toxic look, 32 had hepatomegaly , 5 had splenomegaly, 1 had Icterus, and 1 patient had altered sensorium

Table 9: Shows deranged LFT in comparison to duration of fever in weeks

Duration of fever	No. of patients	Deranged LFT	Percentage	p-value
week 1	31	10	32.3%	.003**
week 2	41	21	51.2%	0.825
week 3	28	15	53.6%	0.262

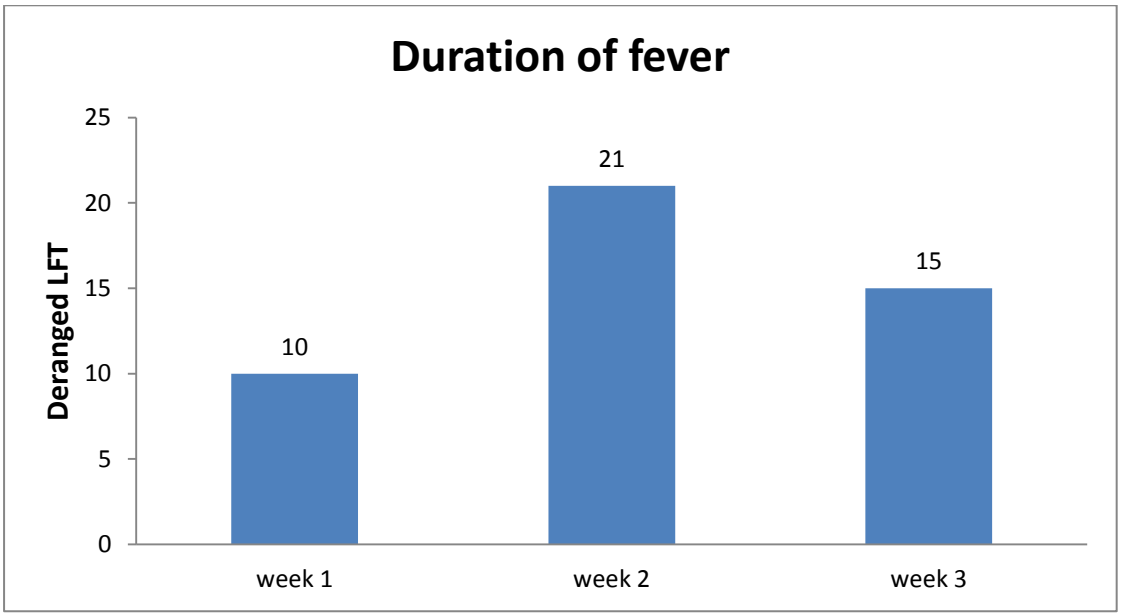

Figure 9: Shows deranged LFT in comparison to duration of fever in weeks

Table 9 - shows in 1st week 10 patients had deranged LFT, in 2nd week 21 patients had derange LFT, and in 3rd week 15 patients had deranged LFT.

Table 10: Shows complications of Enteric fever according to duration of fever in weeks

Duration of fever	No. of patients	Complications	Percentage
week 1	33	2	6.1%
week 2	41	5	12.2%
week 3	26	2	7.7%

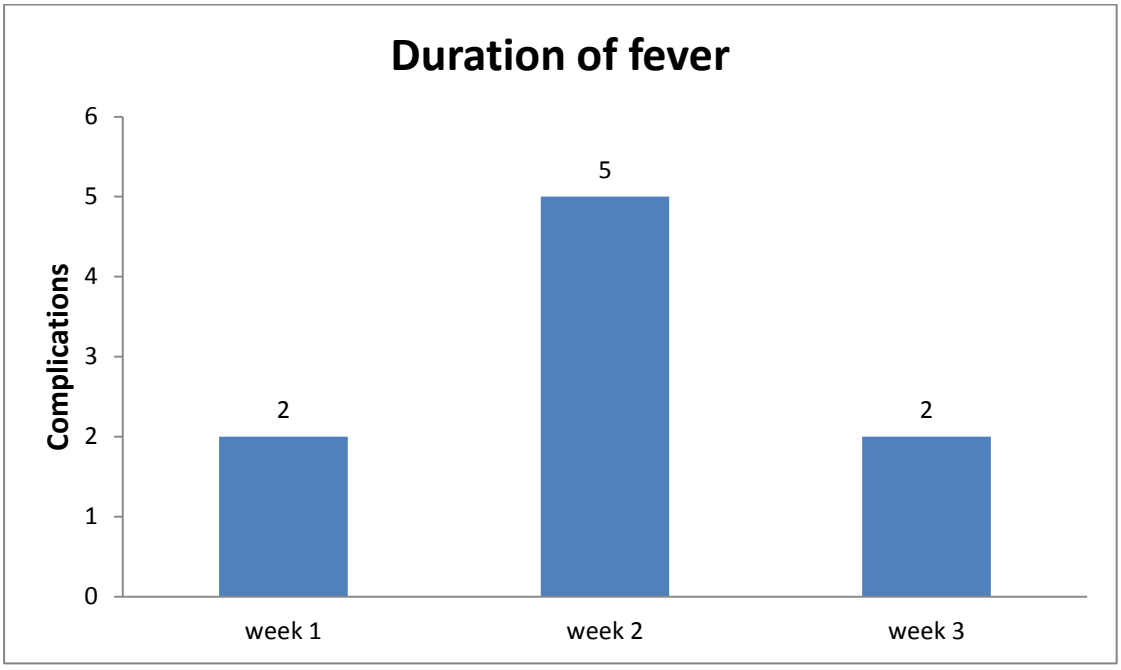

Figure 10: Shows complications of Enteric fever according to duration of fever in weeks

Table 10 - shows 2 patients developed complications in 1st week of fever, 5 Patients developed complications in 2nd week of fever and 2 patients developed complications in 3rd week of fever

DISCUSSION

Salmonella typhi, the bacteria which causes typhoid fever, continues to be a significant threat to public health in many tropical and tropical and subtropical countries with insufficient access to clean water and inadequate sanitation. The gastrointestinal tract serves as the entrance point for the pathogenic organism that causes this febrile and septicemic sickness that affects many systems. As a disease that may be transmitted by the feco-oral route, enteric fever is typically seen in areas with high population densities, inadequate sanitation, and contaminated water. When there is a high prevalence of enteric fever, there is a correlation between insufficient sanitation and a lack of access to safe drinking water. This lack of access makes it difficult to prevent the spread of disease. Enteric fever is more frequent in urban than rural locations in places where it is endemic, and it is also more common in younger age groups.

Enteric fever patients were detected throughout the year in my study, suggesting the endemicity of the disease in this geographical area. Maximum numbers of patients were admitted during May-September, in summer and monsoon seasons. This suggests poor sanitation and poor hygiene is still prevalent and one of the important preventable causative factor for the high prevalence of this tropical infectious disease in this area.

The present prospective observational study was conducted in Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, to study the liver function abnormalities in Enteric fever patients. The study was conducted on the patients who came to Medicine OPD and IPD of Santosh Medical College and hospital. 100 patients were enrolled in the study following the inclusion and exclusion criteria.

Almost one-quarter of the patients in this research exhibited a high titre (1:320) of the serum Widal test. Both the titre of serum widal and hospital admission, is unaffected by factors such as age, gender, or the presence of other medical conditions. There is no correlation found between the rise in titre and an increase in the number of times patients are treated in the hospital. Patients were diagnosed with enteric fever based on their histories and the findings of various investigative parameters. Patients having a history of hepatitis, hepatotoxic medication intake, or liver illness were excluded from the study to exclude any confounding factors. High-grade fever is present in a considerable number of patients (70%), while only 30% of patients had low-grade fever. 70% of patients had chills, and only 30% had

rigors with fever. The classical pattern of enteric fever is stepladder type which was seen in 64% of the patients. Other patterns observed are intermittent and continuous type. G.I. Tract is the most commonly involved system. In 1st week of fever, ALT was raised in 6% of patients, AST was raised in 8% of patients, and ALP was raised in 4% of Patients. In 2nd week of fever duration ALT was raised in 35% of patients, 39% patients had raised AST, and 34% of patients had raised ALP. In patients with 3rd week of fever duration, had raised ALT in 59% of patients, raised AST in 53% of patients, and 62% of patients had raised ALP. Overall, LFT abnormalities were seen in 46% of patients. The most significant signs which correlate with having deranged LFT are hepatomegaly and splenomegaly (P value <0.05). This study shows complications of Enteric fever according to duration of fever in weeks, in 1st week of fever 6.1% of patients suffered from complications, 12.2% in 2nd week of fever, and 7.7% in 3rd week of fever.

Infectious illnesses have a higher incidence rate among younger age groups because the younger population is exposed to a wider range of risk and precipitating factors. In my study, 66% of the study participants were younger than 35 years of age. There was a wide variety of ages represented among the patients, ranging from 18 to 60 years, with a mean age of 28.9 years. The majority of participants in the research were in their second and third decades of life. There were just 10% of the patients who were old aged. In the study of **Dr. Muhammad UsmanAnjum et al.** 59 (51.3%) patients were between the age of 12 to 22 years which is followed by 33 patients (28.7%) in the age group of 23 to 32 years. **Durrani Ab et al.** have also reported a research in which more than 50% of the patients were below 35 years of age. The patients in their research had an average age of 28.5 ±10.14 years. Male dominance was (56 patients) observed in the present study compared to the females (44 patients), and there is no statistically significant difference in the number of male and female patients (P value = 0.098). **Mohammad UsmanAnjumet al.** did a similar study where total 115 cases of patients in the study were taken and there were 63 males (54.8%) and 52 females (45.2%), with a male to female ratio of 1.2:1. **Ashish Kakarial et al.** has similarly reported the same findings, according to the findings the incidence rate was practically same in both sexes. The population with the lower socioeconomic status was the one that was affected the most, which may have been caused by improper sanitation and overcrowding. In this study, it has been shown that there is no significant link between the liver function tests (ALT, AST, and ALP) and symptoms such as fever, pain abdomen, loose stools, and vomiting (P value > 0.05). Similarly, **Srikanth N. MD et al**. conducted a study on 50 patients suffering from

enteric fever. The patients' ages ranged from 14 to 60 years, and the researchers found that a raised AST level of more than twofold was observed in 2 cases during the first week of the illness, 13 cases during the second week, and 7 cases during the third week. There is a correlation that can be supported by statistical analysis that exists between AST levels and the length of a fever. Patients who have had a fever for a considerable amount of time in the past are more likely to have abnormal LFT results.

Rasoolinejad et al. have reported in his study the incidence of jaundice in found to be 24.2% in typhoid patients, **Ahmed and Ahmed et al.** reported it to be 12.2%, contrary to our study where only one patient was icteric. There might be numerous reasons for the wide variation in jaundice incidence among typhoid patients. For instance, patients presenting late at the hospital, using over-the-counter medications for non-specific symptoms, and a lack of healthcare services. This is an important determinant of delayed or missed diagnosis of Enteric fever.

S. Bhatia et al. carried out a research on 111 patients who were diagnosed with enteric fever. Of those 111 individuals, 56 were diagnosed with typhoid fever, and 55 were found to have paratyphoid fever (both at a frequency of 50%). Patients who presented after the second week of illness were more commonly to have elevated levels of liver enzymes; AST values were abnormal in 93 patients, which accounts for 82% of the total patients. On the contrary, in our study 100 patients were diagnosed with enteric fever, out of which majority of patients were diagnosed with typhoid fever 96% cases and only 4% of patients had paratyphoid fever

A research was conducted on patients of the paediatric age range by **Jain H. Et al.** The patients were diagnosed with enteric fever on the basis of clinical symptoms. This diagnosis was verified by the Widal test, and an LFT was performed to determine whether or not the liver was involved. In which there was hepatomegaly present in 35% of patients, and tender hepatomegaly present in 2% of cases. ALT levels were elevated in fifty percent of patients, whereas AST levels were up in forty-six percent of cases. The majority of the subjects presenting with elevated ALT and AST levels did so during the second week of fever. Similarly, in our study, hepatomegaly was present in 39 % of patients, ALT levels were elevated in 41% of patients, and AST levels were elevated in 46% of patients.

CONCLUSION

The present study was conducted in Department of Medicine, Santosh Medical College and hospital, Ghaziabad with the objective to study LFT abnormalities in patients of Enteric Fever. A total of 100 cases were included in the study.The age group of patients is above 18 years of age and there's no significance (P>0.05) found on the basis of gender of the patient. There is no significance (P>0.05) in LFT abnormalities i.e. AST, ALT, ALP in relation to symptoms like Pain abdomen, Loose stool, Vomiting. There was significant difference in ALT, AST, ALP in patients of Hepatomegaly and Splenomegaly (p>0.05). In relation with Relative bradycardia, Toxic look and altered sensorium alone there is no significance. There is significant raise of liver enzymes in patient showing signs like hepatomegaly and splenomegaly (P value<0.05). Complications were found to be in 9% of the patients and the most common complication presented in patients was hepatitis. Complications were more common in 2^{nd} and 3^{rd} week of illness as compared to 1^{st} week of illness. There was significant LFT abnormalities i.e. ALT, AST, and ALP found in the patients of Enteric fever with longer duration of fever (more in 2^{nd} week of fever).

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ANNEXURE-1

CLINICAL PROFORMA

Particulars of the patient:

1. Name:
2. Age:
3. Sex:
4. Occupation:
5. D.O.A:
6. D.O.D:

History:

1. Presenting complaints (with duration, onset, associated factors)
2. Fever with Chills
3. Pain Abdomen
4. Headache
5. Vomiting
6. Loose Stool
7. Cough
8. Altered Sensorium
9. Jaundice
10. History of significant cardiovascular / cerebrovascular disease / thyroid disorder.

Past History:

History of Tuberculosis, Diabetes, CAD, COPD, Asthma, Seizures.

Personal History:

1. Dietary-
2. Sleep-
3. Bladder and bowel-
4. Smoking-
5. Alcohol-
6. Treatment History-

General Physical examination:

1. Built-
2. Nutrition-
3. Pallor/Icterus/Clubbing/Cyanosis/Lymphadenopathy/Oedema
4. BP-
5. Pulse-

6. Respiratory Rate-

SYSTEMIC EXAMINATION:

Abdominal:

- Inspection
- Palpation
- Percussion
- Auscultation

CVS:

- Inspection
- Palpation
- Percussion
- Auscultation

CNS:

- Higher functions
- Sensory System (including Parietal lobe sensations)
- Motor System (including reflexes, abnormal movements)
- Cranial Nerves
- Cerebellar signs
- Meningeal irritation

Respiratory:

- Inspection
- Palpation
- Percussion
- Auscultation

Investigations:

- Liver function test
- Blood Culture
- Widal Test (rising titres)
- Chest X-ray
- Peripheral smear for malaria parasite
- Hepatitis B surface antigen
- Complete hemogram
- Urine for routine examination.
- Ultrasonography (if needed).

ANNEXURE -2

CONSENT FORM

SANTOSH MEDICAL COLLEGE AND HOSPITAL (GHAZIABAD)

I _____ Son/Daughter/Wife of _____ resident of _____. hereby declare that I give my full, free and voluntary informed consent in the thesis **"Study of Liver function abnormalities and its prognostic significance in Enteric fever"** Dr._____ has informed me to my full satisfaction, in the language I understand, about the purpose, nature of study and various laboratory investigations for the study to be carried out. I have been informed about the duration of the study and instructions to be followed during the study period.

I give full consent for being enrolled in the above study and I reserve my rights to withdraw from this study, whenever I wish without prejudice of my right to undergo further treatment at Santosh Hospital, Ghaziabad U.P.

Patient's/ Patient's relative's signature
Or thumb impression

Doctors signature

Name:

Date:

We have witnessed that the patient signed the above form in the presence of his free will after fully understanding its content.

Signature of Witness

Signature of Investigator

Name

Name: **Dr. ABHISHEK SHARMA**
Designation: PG Department of
General Medicine

Contact No.

सहमतिपत्र (सूचित)

संतोष मेडिकल कॉलेज एवं अस्पताल (गाजियाबाद)

मैं _____ बेटा / बेटी /पत्नी_____निवासी _____ घोषणा करता हूं कि मैं

डॉ ._____, ने मुझे मेरी भाषा में अपने अध्ययन **"Study of Liver function abnormalities and its prognostic significance in Enteric fever"** अध्ययन के उद्देश्य के बारे में,और अध्ययन के दौरान अपनाई जाने वाली विभिन्न प्रयोगशाला जांच के बारे में सूचित कर दिया है।मुझे अध्ययन की अवधि और उसके दौरान अपनाए जाने वाले निर्देश भी मेरी भाषा मे समझा दिए गए हैं। मैं उपरोक्त अध्ययन में बिना किसी दबाव के दाखिला ले रहा हूं और पूर्ण सहमति दे रहा हूं। सन्तोष अस्पताल, गाजियाबाद में अपने आगे के उपचार पर बिना प्रतिकूल प्रभाव डाले इस अध्ययन से और प्रयोगशाला जांच की प्रकृति से मैं जब चाहूँ बाहर जाने के अपने अधिकार को सुरक्षित रख रहा हूं।

रोगी / रोगी के रिश्तेदार के हस्ताक्षर डॉक्टर के हस्ताक्षर

नाम

दिनांक:

मेरी उपस्थित मे मरीज ने पूरी तरह से डॉक्टर के बताए गए अध्ययन और निर्देशों को समझने के बाद अपनी स्वतंत्र इच्छा से ऊपर के फार्म पर हस्ताक्षर किए हैं।

हस्ताक्षर

नाम:

पदनाम: पीजी

शल्यचिकित्सा विभाग

SANTOSH MEDICAL COLLEGE & HOSPITAL

Details of Patient Information Sheet
Human Subject Research Proposal

1) Identifying Data

Name of Researcher: Dr. Abhishek Sharma

Department: Department of General medicine and psychiatry

Title of Project: **"Study of Liver function abnormalities and its prognostic significance in Enteric fever"**

2) Description of Human Subjects Safeguards and Rights:

A) Possible psychological or physical risk or discomfort, involved in research
Yes □ NO □ (if no, skip item B)
If yes, answer the following

Why necessary?

1. To have the common disease
2. Specificity and sensitivity of the treatment

B) Make sure the following questions are answered in your research proposal on collection of Data:

1) When will it take place?
July 2021 to June 2022.

2) What length of time needed for complete examination of the patient?
Approximately 1 hour.

3) What period of time needed?
Approximately 1 year.

4) Which specific place within institution?
Department of Medicine.

5) How much population required including number of subject?
100

6) Name of instrument to be used for data collection?

A clinical study on risk factors, clinical presentation,
Liver function test which included total proteins, albumin, total and direct bilirubin, aspartate amino transferase, alanine amino transferase, alkaline phosphatase and Blood culture.

Widal test (rising titres), Chest X-ray, Peripheral smear for malaria parasite, and Hepatitis B surface antigen.

Complete hemogram.

Urine for routine examination and presence of urobilinogen, bile salt and pigments.

Routine blood tests for sugar, urea and creatinine, Ultrasonography of abdomen were done in clinically indicated cases.

7) Methodology to be used (write details)?

- A relevant past medical history, duration of illness, treatment taken for the disease. The data collection included a detailed clinical history, examination, investigations, follow up, the treatment given and complications observed. A past history of fever was looked. A detailed clinical examination to be carry out particularly for the presence of jaundice, pallor, Hepatosplenomegaly, altered sensorium, perforation and bleeding tendencies.

C) Will Subjects be given research results if they so request?

Yes □ No □

ANNEXURE-5

ETHICAL & SCIENTIFIC BOARD COMMITTEE CERTFICATE

SANTOSH
Deemed to be University
(Established u/s 3 of the UGC Act, 1956)

F. No. SU/2021/1830[14] Dated: 17.07.2021

Subject: Grant of Ethical Clearance for Thesis Protocol Topic "**STUDY OF LIVER FUNCTION ABNORMALITIES AND IT'S PROGNOSTIC SIGNIFICANCE IN ENTERIC FEVER",** submitted by **Dr. Abhishek Sharma,** MD/MS student of Batch 2020-2021, Department of **General Medicine**.

*****

With reference to his/her request for grant of Ethical Clearance for the Thesis Protocol entitled **"STUDY OF LIVER FUNCTION ABNORMALITIES AND IT'S PROGNOSTIC SIGNIFICANCE IN ENTERIC FEVER", Dr. Abhishek Sharma** is informed that the Thesis Protocol submitted by him/her was considered by the **Screening Committee** of the Santosh Medical College & Hospital in its meetings held on 19.03.2021, 22.03.2021, 24.03.2021, 25.03.2021, 26.03.2021, 27.03.2021 and 06.04.2021. The recommendations of the **Screening Committee** were considered in detail by the Institutional **Ethics Committee** in its meeting held on **12.07.2021** and the same was **approved** by the **Ethics Committee**.

He /She is informed accordingly for further necessary action.

[Dr. V. P. Gupta]
REGISTRAR

SANTOSH DEEMED TO BE UNIVERSITY ★ REGISTRAR ★ GHAZIABAD, NCR DELHI

Dr. Abhishek Sharma
MD/MS student of batch 2020-2021
Department of General Medicine
Email: doctorabhisheksharma@gmail.com

Copy to:

1. The Vice Chancellor
2. The Dean, SMC&H
3. The Dean – Research
4. The Dean – Academics
5. The Director - IQAC
6. Dr Naresh kumar(Guide)
7. HOD of **General Medicine**

PLAGIARISM REPORT

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INTRODUCTION

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KEY TO MASTER CHART

SEX

Male	1
Female	2

TYPHOID/ PARATYPHOID

Positive	1
Negative	2

FEVER

Present	1
Absent	2

PAIN ABDOMEN

Present	1
Absent	2

VOMITING

Present	1
Absent	2

LOOSE STOOLS

Present	1
Absent	2

RELATIVE BRADYCARDIA

Present	1
Absent	2

TOXIC LOOK

Present	1
Absent	2

ICTERUS

Present	1
Absent	2

HEPATOMEGALY

Present	1
Absent	2

SPLENOMEGALY

Present	1
Absent	2

ALTERED SENSORIUM

Present	1
Absent	2

ALT

Deranged	1
Normal	2

AST

Deranged	1
Normal	2

ALP

Deranged	1
Normal	2

SR. BILLIRUBIN

Deranged	1
Normal	2

BLOOD CULTURE

Positive	1
Negative	2

COMPLICATIONS

No complication	1
Hepatitis	2
Encephalopathy	3
Peumonia	4

DURATION OF FEVER

1st week	1
2nd week	2
3rd week	3

MASTER CHART																				
S. No	**Name**	**Sex**	**Typhoid/ Paratyphoid positive**	**Fever**	**Pain abdomen**	**Vomiting**	**Loose stools**	**Relative Bradycardia**	**Toxic Look**	**Icterus**	**Hepatomegaly**	**Splenomegaly**	**Altered sensorium**	**ALT**	**AST**	**ALP**	**Sr. Billirubin**	**Blood Culture**	**Complications**	**Duration of fever**
1	shobha	1	1	1	2	2	1	2	1	1	1	2	2	1	1	1	1	1	2	2
2	megha	2	1	1	1	1	2	1	1	2	2	2	2	2	2	2	2	1	1	1
3	anjali	2	1	1	1	1	2	2	1	2	2	2	2	1	1	1	2	1	4	2
4	harnoor	2	2	1	1	2	1	2	1	2	1	1	2	2	2	2	2	1	1	1
5	kishan	1	1	1	2	1	2	2	1	2	1	2	2	1	1	1	2	1	1	1
6	mahesh	1	1	1	1	1	1	1	1	2	1	2	2	1	1	1	2	1	1	1
7	umesh	1	2	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1
8	manish	1	1	1	1	1	1	2	1	2	1	2	2	1	1	1	2	1	1	1
9	arun	1	1	1	1	1	1	2	1	2	2	2	2	2	2	2	2	1	1	1
10	arti	2	1	1	1	1	2	2	1	2	2	2	2	2	1	2	2	1	1	1
11	leela devi	2	1	1	2	1	2	2	1	2	2	2	2	1	1	1	2	1	4	3
12	pinki	2	1	1	1	1	2	2	1	2	1	2	2	2	2	2	2	1	1	1
13	Chanderpal	1	1	1	1	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
14	soni	2	1	1	2	2	2	2	1	2	2	2	2	2	1	2	2	1	1	1
15	suresh	1	1	1	2	2	2	2	1	2	1	2	2	1	1	1	1	1	2	1
16	Swati	2	1	1	2	1	1	2	1	2	1	1	2	1	1	1	2	1	1	1
17	sushil	1	1	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	1
18	richa	2	1	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	2
19	anwar jaha	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	1
20	anuradha	2	1	1	2	2	1	1	1	2	2	2	1	1	1	1	1	1	3	3
21	arun	1	1	1	1	1	2	2	1	2	1	2	2	2	2	2	2	1	1	1
22	neha	2	1	1	2	2	2	2	1	2	2	2	2	1	1	1	2	1	4	2
23	yogender	1	1	1	1	1	1	2	1	2	2	2	2	2	2	2	2	1	1	1
24	sandhya	2	1	1	1	1	1	2	1	2	2	2	2	2	1	2	2	1	1	3
25	shanti	2	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	2
26	suresh chand	1	1	1	1	1	1	2	1	2	2	2	2	2	2	2	2	1	1	2
27	soham	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	1
28	shobha	2	1	1	2	2	2	2	1	2	1	2	2	2	2	2	2	1	1	2
29	anil	1	1	1	1	2	2	2	1	2	1	2	2	1	1	1	2	1	1	1
30	leela	2	1	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	2
31	mahesh	1	1	1	1	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
32	shalu	2	1	1	2	2	2	1	1	2	1	1	2	1	1	1	2	1	1	2
33	kavya	2	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	1
34	ankit	1	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	2
35	soni	2	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1
36	sohit	1	1	1	2	2	1	2	1	2	1	2	2	1	1	1	2	1	1	2
37	pooja	2	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
38	raanu	2	1	1	2	2	2	2	1	2	2	2	2	2	1	2	2	1	1	2
39	khushi	2	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
40	priya	2	1	1	2	1	2	2	1	2	1	2	2	1	1	1	2	1	1	2
41	radha	2	1	1	2	2	1	1	1	2	1	2	2	1	1	1	2	1	1	3
42	nitin	1	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1
43	abhinav	1	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1
44	dheeru	1	1	1	2	2	1	2	1	2	1	1	2	1	1	1	2	1	1	2
45	moni	1	2	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
46	vipin	1	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
47	ashish	1	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
48	kalu ram	1	1	1	2	1	2	1	1	2	1	2	2	1	1	1	2	1	1	3
49	bhanu	1	1	1	2	1	2	2	1	2	1	2	2	1	1	1	1	1	2	2
50	shubham	1	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	2
51	naushad	1	1	1	1	1	2	2	1	2	2	2	2	2	2	2	2	1	1	1
52	narender	1	1	1	1	1	2	2	1	2	1	2	2	1	1	1	2	1	1	2
53	madhu rani	2	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	3
54	savita	2	1	1	2	2	1	2	1	2	2	2	2	2	1	2	2	1	1	2
55	mansi	2	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	3
56	vinod	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1
57	rani	2	1	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
58	amit kumar	1	1	1	1	1	2	1	1	2	2	2	2	1	1	2	2	1	1	2
59	satender	1	1	1	1	1	2	2	1	2	1	2	2	1	1	1	2	1	1	3
60	brij pal	1	1	1	2	1	2	2	1	2	1	2	2	1	1	1	2	1	1	2
61	archana	2	1	1	1	1	2	2	1	2	2	2	2	2	2	2	2	1	1	2
62	ravi	1	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	1
63	sadiya noor	2	1	1	2	1	1	2	1	2	2	2	2	1	1	2	2	1	1	2
64	luv kumar	1	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	3
65	poonam	2	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	2

S. No	Name	Sex	Typhoid/ Paratyphoid positive	Fever	Pain abdomen	Vomiting	Loose stools	Relative Bradycardia	Toxic Look	Icterus	Hepatomegaly	Splenomegaly	Altered sensorium	ALT	AST	ALP	Sr. Billirubin	Blood Culture	Complications	Duration of fever
66	amir	1	1	1	2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	3
67	suneeta	2	1	1	2	1	2	1	1	2	2	2	2	2	2	2	2	1	1	2
68	sumitra	2	1	1	1	2	1	2	1	2	1	2	2	1	1	2	2	1	1	2
69	suniel	1	1	1	2	2	1	2	1	2	1	2	2	1	1	1	2	1	1	3
70	vicky	1	1	1	2	2	2	2	1	2	1	2	2	1	1	1	1	1	2	2
71	raj bahadur	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
72	tahir	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	3
73	nisha	2	1	1	2	2	2	1	1	2	2	2	2	2	2	2	2	1	1	3
74	afsar ali	1	1	1	1	2	1	2	1	2	1	2	2	1	1	1	2	1	1	2
75	ruksana	2	1	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	3
76	harsh	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	2	1	1	2
77	sanjay	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	2	1	1	3
78	beena	2	1	1	1	2	2	2	1	2	1	1	2	1	1	1	2	1	1	2
79	gopal	1	1	1	2	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
80	garima	2	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
81	firoza	2	1	1	2	2	2	1	1	2	2	2	2	2	2	2	2	1	1	3
82	maheshwari	2	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
83	anil	1	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	3
84	prabha	2	1	1	1	1	2	2	1	2	2	2	2	2	2	2	2	1	1	2
85	sudesh	1	1	1	2	1	2	2	1	2	1	2	2	1	1	1	1	1	1	3
86	alok	1	1	1	2	1	1	2	1	2	1	2	2	1	1	1	2	1	1	3
87	suresh	1	1	1	1	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
88	bharat	1	1	1	1	2	2	1	1	2	2	2	2	2	2	2	2	1	1	2
89	arun	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
90	meena	2	1	1	1	2	2	2	1	2	1	2	2	1	1	1	2	1	1	3
91	prabha	2	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	3
92	dharam veer	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
93	jonny	1	2	1	2	2	2	2	1	2	1	1	2	1	1	1	1	1	2	1
94	roshni	2	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	3
95	kanti	2	1	1	1	2	1	1	1	2	2	2	2	2	2	2	2	1	1	2
96	shantanu	1	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	3
97	laxmi	2	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
98	krishna	1	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
99	pawan	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	2	1	1	2
100	suraj	1	1	1	1	2	2	2	1	2	1	2	2	1	1	1	2	1	1	2